Sir:

I, Mitsuji AKAZAWA, declare as follows:

I. IDENTIFICATION OF DECLARANT

I am employed by TEIKOKU SEIYAKU CO., LTD and hold the position of associate director of New Product Planning Department.

My educational background is the following:

Graduated from Tokushima University

Bachelor's Degree in Engineering

II. DETAILS OF EXPERIMENTS

I have conducted personally or under my direction and control the following experiments:

1. Preparation of a dosing composition

1) Reagent; 10% suspension of brewer's yeast (suspended in saline so that the concentration of brewer's yeast becomes 10%).

2) Test substance; a patch cut to a 3×4 cm square.

2. Animal used

Rats of Wistar strain (male, 5 weeks old)

3. Test Procedure

(1) Stimulus of pressure was added to a right hind paw of each rat by using a measuring device of pain threshold, and the pain threshold was measured for each rat by determining "biting", "screaming" and "drawing the hinder leg away" as a larvate pain reaction.

Individuals showing the pain threshold of 50 to 61 mmHg were selected and divided into groups consisting of 15 individuals per group.

(2) Each test substance was topically applied and fixed by paper tapes to the right hind paws of the rats. In addition, same operations were conducted except for applying no test substances for a non-treated group.

(3) The test substances were removed after 4 hours of application of the test substances. Then, inflammation was induced by injecting 0.1 ml of brewer's yeast suspension under the skin of a pad of the right

paw.

(4) Pain threshold was measured for each rat 3 hours after the induction of inflammation, whereby the ratio of the pain threshold was obtained according to the following formula (1) and then the rate of increase of the pain threshold for the group dosed test substances based upon that for the non-treated group was calculated according to the following formula (2).

Formula (1); $A = A_1 / A_0$

In the formula (1), A is the ratio of the pain threshold, A_1 is the pain threshold after the brewer's yeast injection and A_0 is the pain threshold before the brewer's yeast injection.

Formula (2); $B\ (\%) = (B_1 - B_0) / B_0 \times 100$

In the formula (2), B is the rate of increase of the pain threshold (%), B_1 is the ratio of the pain threshold for the group dosed each test substance and B_0 is the ratio of the pain threshold for the non-treated group.

4. Examples

1) Example (A) wherein the content of water is 60% by weight and Example (B) wherein the content of water is 20% by weight:

An external skin patch was prepared in the same production process employed in Example 1 except that the amount of each component was shown in Table I.

Table I

	Example(A)	Example(B)
Water content	60%	20%
Ingredients		
Sodium Diclofenac	1	1
Lidocaine	5	5
Propylene Glycol	10	10
N-methyl-2-pyrroridone	5	5
70% Sorbitol solution *	3.1	60.3
Sodium Polyacrylic Acid	5	5
Carboxymethylcellulose Sodium	4	4

Dry Aluminum Hydroxide Gel	0.3	0.3
Tartaric Acid	2.5	2.5
Kaolin	5	5
Water	59.1	1.9

*: 70% sorbitol solution contains 30% of water by weight.

2) Comparative Example (A) of a skin patch with substantially water-free:

An external skin patch which is a substantially water-free film was prepared in the same production process employed in Example 8 of US '363 except that reagents and the concentration of each reagent were same as the above Example (A) and (B) as shown in Table II.

Table II

	Comparative example (A)
Ingredients	
Karaya Gum	40
Polyvinylpyrrolidone	20
Oleic Acid	34
Sodium Dicrofenac	1
Lidocaine	5
Ethanol	(100)

5. Result :

Table III

Examples	Ratio of Pain Threshold	Increase of Pain Threshold (%)
Control (Non-treated)	0.43 ± 0.02	—
Example (A)	0.67 ± 0.01**	55.8
Example (B)	0.66 ± 0.02**	53.5
Comparative Example (A)	0.52 ± 0.02	20.9

Tukey's multiple range test: **; $p<0.01$ (vs. Control)

The above Examples (A), (B) and Comparative Example show that the external skin patches wherein the content of water is 20 to 60% by weight based upon the total weight of the adhesive gel base can achieve superior pain relief effect compared to the external skin patches wherein the content of water is less than 10% by weight as US'363.

III. CONCLUSION

The foregoing experiments demonstrate that the external skin patch according to the claimed invention wherein the content of water is 20 to 60% by weight achieves an unexpectedly superior pain relief effect compared to an external skin patch according to the prior art wherein the content of water is less than 10% by weight.

IV. VERIFICATION CLAUSE

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 12/21/2004 Signature: Miyawa